METHOD FOR DELIVERING A PHARMACEUTICAL COMPOSITION TO PATIENT IN NEED THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority from Provisional Patent Application No. 61/095,584, filed in the United States on Sep. 9, 2008, the entire contents of which is incorporated herein by reference in its entirety.

The present disclosure is directed to a method for delivering a pharmaceutical composition to a patient in need thereof, comprising: administering to said patient a pharmaceutical composition in unit dose form comprising naproxen, or pharmaceutically acceptable salt thereof, and esomeprazole, or pharmaceutically acceptable salt thereof.

Over 15 million Americans take nonsteroidal anti-inflammatory drugs (NSAIDs) each day as a treatment for pain or inflammation. Unfortunately, many of these NSAIDs are associated with a high incidence of gastrointestinal complications, including gastritis, dyspepsia, gastroduodenal ulcers, perforations, and bleeding. A major factor contributing to the development of gastrointestinal lesions appears to be the presence of acid in the stomach and upper small intestines.

During recent years, attempts have been made to reduce the gastrointestinal risk associated with taking NSAIDs by administering agents that inhibit stomach acid secretion, such as, for example, proton pump inhibitors with the NSAID. For example, U.S. Pat. No. 6,926,907 is directed to at least one drug dosage form comprising a proton pump inhibitor that raises the pH of a patient's gastrointestinal tract, followed by an NSAID. This, and similar, formulations can be effective in improving NSAID tolerability through dosages of esomeprazole and naproxen that produce the desired pharmacodynamic response and pharmacokinetic values. Parameters that may influence the desired pharmacodynamic response and pharmacokinetic values include, but are not limited to, for example, the dosage of each; extent of drug absorption; extent of drug distribution, and the duration of drug administration.

There is a need for a clinically effective therapy that delivers to a patient in need thereof a pharmaceutical composition in a unit dose form comprising naproxen, or pharmaceutically acceptable salt thereof, and esomeprazole, or pharmaceutically acceptable salt thereof, for a duration sufficient to achieve an instragastric pH of about 4 or greater and a plasma level of naproxen that is efficacious.

In one aspect, the disclosure is directed to a method for delivering a pharmaceutical composition to a patient in need thereof, comprising: administering to said patient a pharmaceutical composition in unit dose form comprising naproxen, or pharmaceutically acceptable salt thereof, and esomeprazole, or pharmaceutically acceptable salt thereof, wherein said esomeprazole, or pharmaceutically acceptable salt thereof, is released from said unit dose form at a pH of from about 0 or greater to target: a mean % time at which intragastric pH remains at about 4.0 or greater for about a 24 hour period after reaching steady state of at least about 41%.

In another aspect, the disclosure is directed to a method for delivering a pharmaceutical composition to a patient in need thereof, comprising: administering to said patient a pharmaceutical composition in unit dose form comprising naproxen, or pharmaceutically acceptable salt thereof, and esomeprazole, or pharmaceutically acceptable salt thereof, wherein said esomeprazole, or pharmaceutically acceptable salt thereof, is released from said unit dose form at a pH of from about 0 or greater, wherein one unit dose form is administered as an AM dose and a second dose administered about 10 hours later as a PM dose to target

i) a pk profile for naproxen where:
   a) the AM dose has a mean C_{max} of about 81 μg/mL and a median time to maximum concentration (T_{max}) of from about 2.5 to about 4 hours, and
   b) the PM dose has a mean C_{max} of about 76.2 μg/mL and a median T_{max} of from about 10 to about 14 hours; and

ii) a pk profile for esomeprazole where:
   a) the AM dose has a mean area under the plasma concentration-time curve from time zero when the AM dose is administered to about 10 hours after the AM dose is administered ($AUC_{0\text{-}10,am}$) is about 850 hr*μg/mL, and
   b) the PM dose has a mean area under the plasma concentration-time curve from time zero when the PM dose is administered to about 14 hours after the PM dose is administered ($AUC_{0\text{-}14,pm}$) is about 650 hr*μg/mL.

Yet another aspect is directed to delivering a pharmaceutical composition in unit dose form that provides the pharmacodynamic response and/or pharmacokinetic values disclosed herein to a patient being treated for a disease or disorder selected from pain and inflammation.

A further aspect is directed to delivering a pharmaceutical composition in unit dose form that provides the pharmacodynamic response and/or pharmacokinetic values disclosed herein to a patient being treated for osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, or a combination thereof.

A still further aspect is directed to delivering a pharmaceutical composition in unit dose form that provides the pharmacodynamic response and/or pharmacokinetic values disclosed herein to an at risk patient.

Another aspect is directed to delivering a pharmaceutical composition in unit dose form that provides the pharmacodynamic response and/or pharmacokinetic values disclosed herein to an at risk patient being treated for a disease or disorder selected from pain and inflammation.

A further aspect is directed to delivering a pharmaceutical composition in unit dose form that provides the pharmacodynamic response and/or pharmacokinetic values disclosed herein to an at risk patient being treated for osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, or a combination thereof.

Yet another aspect is directed to delivering a pharmaceutical composition in unit dosage form that provides the pharmacodynamic response and/or pharmacokinetic values disclosed herein via a multilayer tablet comprising at least one core and at least a first layer and a second layer, wherein:

i) said core comprises naproxen, or pharmaceutically acceptable salt thereof;
ii) said first layer is a coating that at least begins to release the naproxen, or pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is at about 3.5 or greater; and
iii) said second layer is esomeprazole, or pharmaceutically acceptable salt thereof, wherein said esomeprazole, or pharmaceutically acceptable salt thereof, is released at a pH of from about 0 or greater.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**: Mean pH data over 24 hours on day 9 per protocol population. Treatment A=PN400/E30; B=PN400/E20; C=PN400/E10; D=EC E20+naproxen.